REMARKS

I. Introduction

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the following reasons.

II. Status of the Claims

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

Claims 1, 2, 30, 31, 35, and 36 have been amended to recite "wherein the nanoparticulate drug has an effective average particle size of less than about 1000 nm, wherein at least 50% of the drug particles have **an average** **[[a]]** particle size of less than about 1000 nm . . ." Support for this amendment may be found at, for example, page 14, first paragraph of the specification.

As the foregoing amendments do not introduce new matter, entry thereof by the Examiner is respectfully requested.

III. Responses to Issues Raised by the Examiner in the Outstanding Office Action

A. Rejection of Claims Under 35 U.S.C. § 112, first paragraph

Claims 1-22 and 25-54 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully traverse this ground for rejection.

Applicants respectfully disagree with the Examiner's assertion that the "specification does not provide support for the amended limitation 'wherein at least 50% of the drug particles have a particle size of less than about 1000 nm'" (Office Action at page 2). However, to reduce

the issues and expedite prosecution, claims 1, 2, 30, 31, 35, and 36 have been amended to recite "wherein the nanoparticulate drug has an effective average particle size of less than about 1000 nm, wherein at least 50% of the drug particles have an average particle size of less than about 1000 nm." Support for this amendment can be found at, for example, page 14, first paragraph of the specification.

Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

B. Rejection of Claims Under 35 U.S.C. § 112, first paragraph

Claims 10-12 and 54 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse this ground for rejection.

The Examiner asserts that the specification "does not reasonably provide enablement for using polyvinyl pyrrolidone or polyethylene glycol alone ... capable of controlling release rate" (Office Action, page 3). Contrary to the Examiner's assertion, it is well-established in the formulation arts that water soluble polymers such as polyvinyl pyrrolidone (PVP) can be used as rate-controlling polymers in controlled-release formulations. See Chang (submitted with Applicants' response and entered into the record on September 10, 2001) at page 238, first paragraph.

It is well-known that water soluble polymers can control release of a drug substance. In one example, a water soluble polymer is used in the formation of a hydrophilic matrix. Such a hydrophic matrix controls release of a drug substance contained therein through the formation of a hydrogel upon immersion of the matrix in aqueous media. The hydrogel then slows the release of drug. See Chang at page 238, first paragraph,

> The hydrophilic matrix requires water to activate the release mechanism.... Upon immersion in water, the hydrophilic matrix quickly forms a gel layer around the tablet. Drug release is

> controlled by a gel diffusional barrier that is formed and/or tablet erosion.

Thus, matrix controlled release systems, for example, can use a water soluble polymer as the rate controlling polymer. In general, such polymers have a molecular weight high enough to form a viscous hydrogel. Indeed, as taught by Chang at page 238, fifth paragraph,

> Viscosity characteristics of the polymers are of great importance in determining the final release properties of the matrix tablet. Generally the drug-release rate is slower for a higher viscosity-grade polymer.

Water soluble polymers such as PVP, HPC, and HPMC have varying "grades" or molecular weights. The high molecular weight polymers are very viscous, and therefore, form strong, viscous gels which control the diffusion of water and drug release. This produces a formulation having sustained release properties. For example, PVP (Plasdone povidone), is available in a range of molecular weight from 10,000 (e.g., Plasdone C-15) to 1,300,000 (e.g., Plasdone K-90) and exhibits a viscosity in aqueous solution that is dependent on molecular weight. In particular, Plasdone K-90 is approximately 2 orders of magnitude more viscous at a concentration of 10% (*See* e.g., p. 4 of Plasdone® Povidone Product Guide, International Specialty Products (2005) submitted with Applicants' Request for Continued Examination on January 18, 2006 as EXHIBIT 1). Accordingly, such a polymer would be expected to function as a rate controlling polymer.

Thus, the use of water soluble polymers such as polyvinyl pyrrolidone and polyethylene glycol as rate controlling polymers is fully enabled by the present disclosure and that which was known in the art at the time of filing. Accordingly, reconsideration and withdrawal of this ground of rejection are respectfully requested.

C. Rejections of Claims Under 35 U.S.C. § 102(b)

1. Desieno Fails to Teach or Suggest Rate Controlling Polymers

Claims 1, 2, 8-10, 13, 14, 30, 31, and 34-53 are rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by U.S. Pat. No. 5,573,783 to Desieno et al. ("Desieno"). Applicants respectfully traverse this ground for rejection

The claimed invention is directed to controlled release nanoparticulate compositions. These compositions comprise a poorly soluble nanoparticulate drug, having a surface stabilizer associated with surface of the nanoparticle, and a rate-controlling polymer. Such compositions provide controlled release of the drug from 2 to 24 hours.

In maintaining this rejection, the Examiner continued to rely upon Desieno for its disclosure of a polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG) film coating, "namely, the [claimed] rate-controlling polymer."

a. In Contrast to the Claimed Invention, Desieno Teaches *Rapid Release* Nanoparticulate Compositions

Desieno does not anticipate the claimed invention because the reference explicitly characterizes the PVP/PEG film coat as not impeding the redispersion of drug nanoparticles. Indeed, Desieno flatly states that the disclosed compositions, by contrast to the claimed composition, are not inhibited from redispersing. See col. 18, lines 4-8,

> It has been found that the PVP/PEG overcoat for compositions containing danazol, PVP and sodium lauryl sulfate coated on a bead, in particular, provides physical protection for the drug layer coated on the bead *without inhibiting redispersion* of the drug in aqueous media. (emphasis added)

As evidence of the fast release properties of the Desieno compositions, Desieno describes a procedure to determine the ease of reconstituting particles from the disclosed compositions, *i.e.*, to evaluate the rate of drug particle release. (*See* Desieno at col. 17, line 55, to col. 18, line

3.) Prescribed in this method is a shaking time of 10 minutes, which was sufficient for Desieno to conclude that a PVP/PEG overcoat "in particular . . . [does not] inhibit[] redispersion of the drug in aqueous media." *Id.* at col. 18, lines 4-8. Thus, a person who is skilled in the art reading Desieno therefore would conclude that the PVP/PEG overcoat taught by Desieno is *not* a rate-controlling polymer.

In contrast to these results, Applicants disclose numerous examples of compositions showing sustained drug release, as determining using a procedure (*see* specification at page 24, lines 9-19) analogous Desieno's procedure, over a period of time exceeding the minimum 2 hours as required by the present claims.

b. The compositions of the claimed invention require the release of drug over a time period of 2 to 24 hours.

The Examiner acknowledges that Desieno does not expressly teach the time period of release as being from about 2 to about 24 hours. However, the Examiner concludes that the presence of the PVP/PEG in the compositions of Desieno inherently imbues controlled release properties to the disclosed compositions (Office Action at page 6). However, in reaching this conclusion, the Examiner disregards Desieno's explicit teaching of a rapid release composition, as argued above. Moreover, the Examiner fails to consider that which is known in the formulation arts, namely, that PVP and PEG can be used in both rapid release formulations as well as in controlled release formulations.

i. The formulation arts teach That PVP and PEG overcoats result in rapid release compositions

The formulation arts teach that a PVP/PEG film coating, as with Desieno, can be employed for the manufacture of *rapid release* compositions. "Water-soluble film formers such as . . . polyethylene glycol[] [and] polyvinyl pyrrolidone . . . form a rapidly dissolving barrier. *See* Chang et al. at 216 (submitted with Applicants' response and entered into the record on September 10, 2001). More specific evidence in the art establishes that polyvinylpyrrolidone polymers "are completely soluble in water at room temperature. The maximum concentration of

polymer soluble in water is limited by the viscosity at a given concentration. The viscosity of an aqueous solution depends on the molecular weight of the polymer, with the lower molecular weight having the least effect on aqueous viscosity relative to the higher molecular weight materials." *See* Plasdone® Povidone Product Guide, International Specialty Products (2005) (submitted with Applicants' Request for Continued Examination on January 18, 2006 as EXHIBIT 1). Thus, one of skill in the art would expect that lower molecular weight PVP polymers would be more soluble than higher molecular weight PVP and therefore more amenable to rapid release formulations.

The formulation arts further teach that water soluble polymers can be used in controlled release formulations. In particular, Chang teaches that controlled release formulations can be achieved using, for example, a hydrophilic matrix formulation. Such matrices can comprise water soluble polymers such as polyethylene oxide or polyvinyl pyrrolidone as matrix materials. These matrices rely on the ability of the polymer to form a gel layer around the drug substance upon immersion in water. Such a gel layer provides a diffusional barrier that that, in part, controls drug release. Chang further teaches that the viscosity of the polymer is important in determining the release rate properties of the final matrix and that, in general, drug release rate is slower for higher viscosity (i.e., higher molecular weight) polymers. *See* Chang at p. 238. Thus, when used as a rate-controlling polymer, one of skill in the art would expect that a high molecular weight polymer would be employed.

ii. Applicants' Use of PVP and PEG as Rate Controlling Polymers

The choice of a rate controlling polymer first depends upon the type of controlled release system to be utilized: *i.e.*, a coating system or a matrix system. See claim 1(b)(i) ("the rate-controlling polymer is integrated in a rate-controlling matrix with the nanoparticulate drug composition or coats the nanoparticulate drug composition"; or the composition can comprise both a matrix and a coating system). A rate controlling composition utilizing a coating system employs a polymer that forms a water insoluble backbone, such as poly(alkylmethacrylate), as a rate controlling polymer. Low molecular weight water-soluble polymers of PVP and PEG, can

also be used in coating systems, but in this context they must be used in conjunction with a polymer that forms a water insoluble backbone to yield a controlled release composition. *See e.g.,* Declaration under 37 C.F.R. § 1.132 by Rajeev A. Jain, filed with Applicants' response on January 15, 2003. Thus, if low molecular weight water-soluble polymers PVP and PEG are utilized in a coating system in the absence of a polymer that forms a water insoluble backbone, the resulting composition is an immediate release composition, such as that described by Desieno.

Matrix controlled release systems can use as a rate controlling polymer a water soluble polymer having a molecular weight high enough to form a viscous hydrogel. Water soluble polymers such as HPC and HPMC have varying "grades" or molecular weights; high molecular weight polymers are very viscous, and strong, viscous gels resulting from such polymers control the diffusion of water and drug release, producing rate controlling properties. See e.g., pp. 2, 6-7, and 12 of "Formulating for Controlled Release with METHOCEL Premium Cellulose Ethers," The Dow Chemical Company (1995) (EXHIBIT 2). Thus, the use of a high molecular weight water soluble polymer is used as a rate controlling polymer in a matrix controlled release system.

Therefore, well-established wisdom in the art thus confirms the fact that Desieno does not explicitly or inherently teach controlled release nanoparticulate compositions. Indeed, the rapid release compositions are fully consistent with the use of low molecular weight PVP/PEG overcoats. Furthermore, the controlled release compositions of the present claims are consistent with the use of, for example, PVP or PEG as a rate-controlling polymer. Thus, the compositions of the present application are distinguished over Desieno with respect to the use of PVP or PEG as a rate controlling polymer. Therefore, Desieno does not anticipate the claims. Applicants therefore respectfully urge the PTO to reconsider and withdraw this ground for rejection.

2. Modi Fails to Teach the Recited Nanoparticulate Drug Compositions

Claims 1, 2, 8, 9, 13, 14, 30, 31, 34-38, 41, 42, 45, 46, 49, 50, and 53 are rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by WO 95/22318 to Modi. Applicants respectfully traverse for at least already of record and those that follow.

Modi fails to teach or suggest the claimed requirement that at least one surface stabilizer is associated with the surface of the nanoparticulate drug. The Examiner asserts that Modi at page 5, lines 9-10, "discloses adding surfactant before coating the microspheres with rate controlling polymer" (Office Action at page 11). In response to this assertion, Applicants respectfully direct the Examiner's attention to the text immediately preceding the cited text (i.e., page 5, lines 1-8), wherein Modi discloses that the active ingredient is added to a solution of at least two water soluble polymers, mixed with an emulsifying medium, and homogenized to form a suspension of microdroplets of drug-polymer. Modi states that "[t]he purpose of the surfactant is to prevent agglomeration of the *polymer matrix*" (emphasis added). *See* Modi at page 8, lines 20-21. In contrast, the claimed invention requires a nanoparticulate drug and a surface stabilizer associated with the surface of the drug nanoparticle. Thus, in the case of the claimed invention the surface stabilizer acts to prevent the agglomeration of the *drug*, thus allowing the formation of stable drug nanoparticles.

Modi generally describes the size of the polymer matrix microspheres as on the order of 100-100,000 nm (*see* Modi at page 8, lines 23-25). The reference does not teach or suggest, however, that at least 50% of the drug particles have an average particle size of less than about 1000 nm when measured by light scattering techniques, as required by the claims as amended herein.

Because Modi fails to teach or suggest all of these features of the claimed invention, it does not anticipate. Accordingly, Applicants respectfully request reconsideration and withdrawal of this ground for rejection.

D. Rejection of Claims Under 35 U.S.C. § 103(a)

Claims 1-22 and 25-53 are rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Desieno in view of U.S. Pat. No. 5,145,684 to Liversidge et al. ("Liversidge) and U.S. Pat. No. 5,811,388 to Friend et al. ("Friend"). Applicants respectfully traverse this ground of rejection.

1. Liversidge and Friend do not cure the deficiencies of Desieno because neither teach controlled release nanoparticulate formulations.

As argued above, Desieno teaches rapid release of nanoparticulate active agent compositions but does not teach controlled release nanoparticulate active agent compositions. Liversidge or Friend alone or in combination cannot cure the deficiencies of Desieno because neither teach controlled release of nanoparticulate active agent compositions.

Liversidge teaches nanoparticulate compositions of poorly soluble substances that exhibit high bioavailability. Indeed, the point of making nanoparticulate compositions of poorly soluble drugs is to overcome their inherently slow release and therefore low bioavailability properties. *See e.g.,* Liversidge at col. 1, lines 13-27. Liversidge is silent with respect to controlled release compositions.

Friend teaches *delayed release* compositions for "orally delivering a therapeutically effective amount of drug to the lower GI tract, particularly the colon, without significant release of drug in the upper GI tract" (col. 3, lines 54-57). Such compositions are in contrast to the controlled release or sustained release compositions of the present application. Indeed, Friend describes the difference between delayed release and sustained release at, for example, col. 4, line 60 to col. 5, line 6,

> The compositions and methods of this invention are of a delayed release nature (as compared to sustained or extended release) .... Thus, for purposes of this application a delayed release composition allows for the release of most of the active ingredient in the lower GI, particularly the colon without releasing any

> significant amount of the drug in the upper GI tract as the composition travels through the entire GI tract. *This is different than a sustained release composition that releases the active on a regular (i.e. constant) basis throughout the GI.* (emphasis added)

Thus, Friend does not cure the deficiencies of Desieno because it does not teach sustained release compositions.

Moreover, the claims are patentable over Desieno, Liversidge, and Friend because there is no motivation for the skilled artisan to make the cited combination in order to achieve a controlled release composition. The ordinary artisan would have clearly understood that the nanoparticulate composition comprising a PVP/PEG film overcoating taught by Desieno rapidly releases (*e.g.*, 10 minutes) nanoparticulate drug, where PVP/PEG is not a rate controlling polymer combination. Additionally, both Desieno and Liversidge highlight a central feature of nanoparticulate drug formulations as providing immediate and fast release of the drug. *See* Liversidge at col. 1, lines 28-30; Desieno at col. 1, lines 30-33. *See also* Desieno at col. 8, lines 42-44 ("pharmaceutical compositions of this invention give rise to unexpectedly high bioavailability . . . and rapid onset of drug action"). Friend, on the other hand, teaches delayed release compositions. Therefore, the person of ordinary skill, armed with Desieno, Liversidge, and Friend, would have been motivated, if anything, to make nanoparticulate compositions in the manner prescribed by the references precisely to exploit their rapid release characteristics (*e.g.*, minutes) or delayed release characteristics.

Desieno, alone or in combination with Liversidge and Friend, would not have suggested to the person of ordinary skill a controlled release nanoparticulate drug composition. Thus, the person of ordinary skill in the art would not have considered the claimed invention to be obvious over Desieno, Liversidge, and Friend. Accordingly, Applicants respectfully urge the PTO reconsider and withdraw this ground for rejection.

IV. Conclusion

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. Examiner Tran is invited to contact the undersigned by telephone if she feels that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.